

### **AMENDMENTS TO THE CLAIMS**

Amendments to the claims are reflected in the following listing of claims, which replaces all prior versions and listings of claims.

1. (Currently amended) A method of screening colon tissue for a ~~pathological condition~~ colon cancer, said method comprising:

measuring Prox-1 expression or activity in a biological sample that comprises colon tissue from a mammalian subject, and screening for colon cancer from the measuring of the Prox-1 expression or activity, wherein elevated Prox-1 expression or activity in the colon tissue correlates with a ~~pathological phenotype~~ the presence of colon cancer in colon tissue.

2. (Currently amended) A method according to claim 1, comprising comparing Prox-1 expression or activity in the colon tissue to Prox-1 expression or activity in healthy colon tissue, wherein increased Prox-1 expression or activity in the colon tissue from the mammalian subject correlates with a ~~pathological phenotype~~ the presence of colon cancer in colon tissue.

3. (Previously presented) A method according to claim 2, further comprising a step, prior to said measuring step, of obtaining the biological sample comprising colon tissue from a mammalian subject.

4. (Currently amended) The method according to claim 1, wherein the measuring comprises measuring pathological condition is colon cancer, and wherein increased Prox-1 expression or activity in the colon tissue is indicative of a cancerous or precancerous condition.

5. (Previously presented) The method according to claim 1, wherein the measuring comprises measuring Prox-1 protein in the biological sample.

6. (Original) The method of claim 5, wherein the measuring comprises contacting the colon tissue with a Prox-1 antibody or antigen-binding fragment thereof.

7. (Previously presented) The method of claim 1, wherein the measuring comprises measuring Prox-1 mRNA in the colon tissue.

8. (Original) The method of claim 7, wherein the measuring comprises *in situ* hybridization to measure Prox-1 mRNA in the colon sample.

9. (Original) The method of claim 7, wherein the measuring comprises steps of isolating mRNA from the colon tissue and measuring Prox-1 mRNA in the isolated mRNA.

10. (Previously presented) The method according to claim 1, wherein the measuring comprises quantitative polymerase chain reaction (PCR) to quantify Prox-1 mRNA in the colon tissue relative to Prox-1 mRNA in healthy colon tissue.

11. (Currently amended) A method according to claim 1, further comprising measuring expression or activity of at least one gene selected from the group consisting of CD44, Enc1, and ID2 in the colon tissue, and screening for colon cancer from the measuring of the Prox-1 expression or activity and from the measuring of the expression or activity of the at least one gene, wherein elevated Prox-1 expression or activity and elevated expression or activity of the at least one gene in the colon tissue correlate with the presence of colon cancer in colon tissue a pathological phenotype.

12. (Currently amended) A method according to claim 1, further comprising measuring activation of β-catenin/TCF pathway in the colon tissue, and screening for colon cancer from the measuring of the Prox-1 expression or activity and from the measuring of activation of β-catenin/TCF pathway, wherein activation of the β-catenin/TCF pathway and elevated Prox-1 expression or activity in the colon tissue correlate with the presence of colon cancer in the colon tissue a pathological phenotype.

13. (Original) A method according to claim 12, wherein activation of the β-catenin/TCF pathway is measured by at least one indicator in the colon tissue selected from the group consisting of: mutations in an APC gene; mutations in a β-catenin gene; and nuclear localization of β-catenin.

14. (Previously presented) The method according to claim 1, wherein the mammalian subject is a human.

15. (Currently amended) A method according to claim 14, further comprising a step of administering to a human subject identified as having a colon cancer pathological condition characterized by increased Prox-1 expression or activity in colon tissue a composition comprising a Prox-1 inhibitor.

16. (Canceled)

17. (Withdrawn) A method of inhibiting the growth of colorectal cancer cells in a mammalian subject comprising the step of:

administering to the subject a composition comprising a molecule that suppresses expression or activity of Prox-1, thereby inhibiting the growth of colon carcinoma cells.

18.-20. (Canceled)

21. (Withdrawn) The method according to claim 17, wherein the composition further comprises a pharmaceutically acceptable diluent, adjuvant, or carrier medium.

22. (Withdrawn) The method according to claim 17, wherein the molecule comprises a nucleic acid selected from the group consisting of an antisense oligonucleotide that inhibits Prox-1 expression; micro-RNA that inhibits Prox-1 expression; short interfering RNA (siRNA) that inhibits Prox-1 expression; and short hairpin RNA (shRNA) that inhibits Prox-1 expression.

23.-24. (Canceled)

25. (Withdrawn) The method or use of claim 22, wherein the siRNA comprises at least one nucleotide sequence set forth in SEQ ID NOS: 4, 5, 6, and 7.

26. (Withdrawn) The method of claim 17, wherein the molecule comprises a zinc finger protein that inhibits Prox-1 expression.

27. (Withdrawn) The method of claim 17, wherein the molecule comprises a dominant negative form of Prox-1 protein, or an expression vector containing a nucleotide sequence encoding the dominant negative Prox-1 protein.

28. (Withdrawn) The method of claim 27, wherein the dominant negative form of Prox-1 protein has a disrupted DNA binding domain.

29. (Withdrawn) The method of claim 27, wherein the dominant negative form of Prox-1 protein has a disrupted transactivation domain.

30. (Canceled)

31. (Withdrawn) The method according to claim 17, wherein the composition is administered in an amount effective to suppress Prox-1 expression or activity and increase Notch 1 signaling.

32. (Canceled)

33. (Withdrawn) The method according to claim 17, wherein the composition is administered in an amount effective to increase 15-PDGH activity or decrease prostaglandin D2 synthase activity.

34. (Withdrawn) The method according to claim 17, further comprising administering to the subject an inhibitor of the  $\beta$ -catenin/TCF signaling pathway.

35. (Canceled)

36. (Withdrawn) The method of claim 34, wherein the inhibitor of the  $\beta$ -catenin/TCF signaling pathway is dominant negative form of TCF-4.

37. (Withdrawn) The method of claim 34, wherein the inhibitor of the  $\beta$ -catenin/TCF signaling pathway targets TCF-4,  $\beta$ -catenin, or c-myc.

38. (Withdrawn) The method of claim 17, further comprising administering to the subject a COX-2 inhibitor.

39.-40. (Canceled)

41. (Withdrawn) The method of claim 17, further comprising administering to the subject a Notch signaling pathway agonist.

42.-45. (Canceled)

46. (Withdrawn -- currently amended) A method of inhibiting Prox-1 function in a mammalian subject having a colon cancer ~~disease~~ characterized by Prox-1 overexpression in cells, comprising the step of administering to said mammalian subject a composition, said composition comprising a compound effective to inhibit Prox-1 function in cells.

47. (Canceled)

48. (Withdrawn) A method of screening for a Prox-1 modulator, comprising steps of:

contacting a test molecule with Prox-1 protein, or a nucleic acid comprising a nucleotide sequence that encodes Prox-1 protein, under conditions which permit the interaction of the test molecule with the Prox-1 protein or nucleic acid;

and measuring interaction between the test molecule and Prox-1 protein or nucleic acid, wherein a test molecule that binds the Prox-1 protein or nucleic acid is identified as a Prox-1 modulator.

49.-51. (Canceled)

52. (Withdrawn) A method of screening for modulators of binding between a DNA and Prox-1 protein comprising steps of:

a) contacting a DNA with a Prox-1 protein in the presence and in the absence of a putative modulator compound;

b) detecting binding between the DNA and the Prox-1 protein in the presence and absence of the putative modulator compound; and

c) identifying a modulator compound based on a decrease or increase in binding between the DNA and the Prox-1 protein in the presence of the putative modulator compound, as compared to binding in the absence of the putative modulator compound.

53. (Canceled)

54. (Withdrawn) A method according to claim 48, further comprising steps of:

contacting a cell from a colorectal cancer or colorectal cancer cell line with the Prox-1 modulator; and

selecting a Prox-1 modulator that inhibits growth of the cell.

55. (Withdrawn) A method according to claim 54, further comprising: formulating a composition comprising the selected Prox-1 modulator and a pharmaceutically acceptable carrier; administering the composition to a mammalian subject having a colorectal cancer; and

monitoring the mammalian subject for growth, metastasis, shrinkage, or disappearance of the colorectal cancer.

56.-67. (Canceled)

68. (Withdrawn) The method of claim 17, wherein the molecule comprises a compound comprising a nucleic acid 8 to 50 nucleotides in length, wherein said compound specifically hybridizes with a polynucleotide encoding Prox-1, or hybridizes to the complement of the polynucleotide, and inhibits the expression of Prox-1 when introduced into a cell that expresses Prox-1.

69. (Canceled)

70. (Withdrawn) The method of claim 22, wherein the antisense oligonucleotide has a sequence complementary to a fragment of SEQ ID NO: 1.

71. (Withdrawn) The method of claim 70, wherein the fragment of SEQ ID NO: 1 comprises a promoter or other control region, an exon, an intron, or an exon-intron boundary.

72. (Withdrawn) The method of claim 70, wherein the fragment of SEQ ID NO: 1 comprises an exon-intron splice junction.

73. (Withdrawn) The method of claim 70, wherein the fragment of SEQ ID NO: 1 comprises a region within 50-200 bases of an exon-intron splice junction.

74. (Withdrawn) The method of claim 17, wherein the molecule comprises an inhibitor of DNA methyltransferases, thereby inhibiting Prox-1 expression.

75. (Withdrawn) The method according to claim 74, wherein the inhibitor of DNA methyltransferases is 5-aza-2'-deoxycytidine.

76. (Withdrawn) The method according to claim 22, further comprising administering to the subject an inhibitor of DNA methyltransferases.

77.-78. (Canceled)

79. (Currently amended) The method according to claim 1, wherein the mammalian subject is human, and wherein the method further comprises 4, further comprising diagnosing [[a]] the human subject with respect to a cancerous or precancerous condition of the colon, wherein increased Prox-1 expression or activity in the colon tissue is indicative of a cancerous or precancerous condition.

80. (New) The method of claim 17, wherein the mammalian subject is human.

81. (New) The method of claim 46, wherein the mammalian subject is human.

82. (New) A method of selecting patients for therapy with a Prox-1 inhibitor comprising: (a) screening colon cancer from a mammalian subject for elevated

Prox-1 expression; and (b) selecting for treatment with a Prox-1 inhibitor a mammalian subject identified according to (a) as having elevated Prox-1 expression in colon cancer cells.

83. (New) A method according to claim 82, comprising comparing Prox-1 expression in the colon cancer to Prox-1 expression or activity in healthy colon tissue, wherein increased Prox-1 expression or activity in the colon cancer is identified as elevated Prox-1 expression.

84. (New) A method according to claim 83, further comprising a step, prior to said measuring step, of obtaining a biological sample comprising colon tissue from a mammalian subject.

85. (New) The method of claim 82, further comprising administering to a mammalian subject identified as having colon cancer with elevated Prox-1 expression a Prox-1 inhibitor selected from the group consisting of: an antisense oligonucleotide that inhibits Prox-1 expression; micro-RNA that inhibits Prox-1 expression; short interfering RNA (siRNA) that inhibits Prox-1 expression; short hairpin RNA (shRNA) that inhibits Prox-1 expression; a zinc finger protein that inhibits Prox-1 expression; a dominant negative form of Prox-1 protein, and an expression vector containing a nucleotide sequence encoding the dominant negative Prox-1 protein.